CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-689 [SRL 1 S-001] SUBMISSION DATE: SEPTEMBER 23, 1997
Posicor® (mibefradil hydrochloride) Tablets

HOFFMANN-LA ROCHE

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TYPE OF SUBMISSION: LABELING / DEAR DOCTOR LETTER / TALK PAPER

BACKGROUND:
Mibefradil is a calcium channel blocker approved for the treatment of hypertension and angina. There were recent reports of serious adverse drug reactions resulting from possible interaction between mibefradil and the HMG-CoA reductase inhibitors (the statins). The sponsor was therefore requested to update mibefradil labeling to reflect this additional information.

SUMMARY:
After several meetings within the Agency and with the sponsor agreements were reached on the labeling update, Dear Doctor Letter and FDA Talk paper for the interaction between mibefradil and the various HMG-CoA reductase inhibitors (copies attached).

CONCLUSION:
The Division of Pharmaceutical Evaluation I was involved in the writing of the labeling update, Dear Doctor Letter and FDA Talk paper to reflect the interaction between mibefradil and the HMG-CoA reductase inhibitors.

/S/ 1/4/98
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FT Initialed by A. Parekh, Ph.D. /S/ 1/4/98

cc: NDA 20-689, HFD-110, HFD-860 (Fadiran, Parekh), CDR (Attn: Barbara Murphy)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research

BACKGROUND: POSICOR LABELING CHANGES

Talk Paper	MedWatch

What is Posicor?

Posicor (mibefradil) is a calcium-channel blocker chemically unrelated to the ten other approved calcium-channel blockers. Posicor was approved on June 20, 1997 for treatment of hypertension and angina. Since the drug's market introduction in August 1997, more than 80,000 patients have been treated with the drug.

What determines normal heart rates?

The normal heartbeat is generated by electrical impulses that start in part of the heart called the sinus node, an internal pacemaker.

What causes lowered heart rate?

If the sinus node slows or stops, the heart will usually continue beating, because another part of the heart will take over the job of pacing. These other parts of the heart have natural rhythms that are slower than that of the sinus node, so the resulting heart rate is generally slower than a normal rate, sometimes so much slower that the patient may lose consciousness or even die.

How does Posicor affect the sinus node?

Like several other commonly-used drugs, including all beta-blockers, two calcium channel blockers (verapamil and diltiazem), and digoxin; Posicor can suppress the activity of the sinus node. This drug effect is most frequently seen in patients with preexisting sinus-node disease, but it can also occur in otherwise healthy people, especially in elderly women. When two or more of these drugs are taken at the same time, the risk of extreme slowing of the heart rate is greater than the risk when either drug is taken separately.

BACKGROUND: MUSCLE INJURY

How does Posicor interact with other drugs?

A liver enzyme called CYP3A4 is responsible for the metabolic elimination of many drugs. Like many drugs and some foods, Posicor suppresses the activity of CYP3A4. When the enzyme is inactive, drugs that depend on it for their metabolism and elimination accumulate within the body, possibly increasing the likelihood of adverse effects.

Because of this known effect of Posicor, the original labeling of Posicor stated that coadministration of Posicor was contraindicated with astemizole, cisapride, or terfenadine. These drugs, normally eliminated by CYP3A4 can accumulate to dangerous levels when Posicor is coadministered.

What are statins (Cholesterol-lowering drugs)?

The class of drugs known as the statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) are cholesterol-lowering drugs from the drug class known as S-hydroxy-3

methylglutaryl-coenzyme-A-reductase inhibitors. This unwieldy designation is sometimes shortened to "HMG CoA reductase inhibitors," but more often these drugs are collectively referred to as "statins" from their shared generic suffix.

What are the calcineurin immunosuppressants?

Tacrolimus (FK506) marketed as Prograf (Fujisawa) and cyclosporine marketed as Sandimmune and Neoral (Sandoz) are known as calcineurin immunosuppressants. These drugs are given to transplant recipients to prevent rejection of their transplanted organs.

What is rhabdomyolysis?

The muscle of the body includes that of the heart; the "smooth" muscle that forms part of the wall of the blood vessels and gut; and the remaining muscles, which are called the "skeletal" muscles. When skeletal muscle disintegrates, the process is known as rhabdomyolysis.

Rhabdomyolysis is usually accompanied by pain, tenderness, and weakness in the affected muscles. The most important consequences of rhabdomyolysis, however, are not those on the muscle themselves. As muscle cells break down, they release substances that can cause injury to the kidneys, sometimes permanent but even when reversible, sometimes requiring temporary hemodialysis. If muscle cells break down rapidly enough, released potassium can cause lethal malfunction of the heart.

Rhabdomyolysis occurs in a large number of medical conditions, including crushing injuries, heat stroke, diabetic crises, and Legionnaire's disease. Rhabdomyolysis is also an occasional side effect of any of a large variety of common drugs and toxins. Rhabdomyolysis is not known to be associated with Posicor alone or any other calcium-channel blocker.

Posicor, Statins and Rhabdomyolysis: The statins are not all identically metabolized. In particular, fluvastatin and pravastatin are metabolized by processes that are independent of the enzyme CYP3A4. There have been no reported cases of rhabdomyolysis seen after coadministration of either of these drugs with Posicor, and Posicor would not be expected to increase the incidence of rhabdomyolysis associated with fluvastatin and pravastatin.

Atorvastatin and cerivastatin are each metabolized by CYP34A but some of the products of this metabolism are similar in effect to the original drugs. For this and other technical reasons, important interactions with mibefradil are unlikely. There have been no reported cases of muscle injury after coadministration of Posicor and atorvastatin or cerivastatin (only recently marketed). Nevertheless coadministration of Posicor with these two drugs should generally be avoided until more is known.

Lovastatin and simvastatin are dependent on CYP34A for their metabolism. In normal volunteers inhibition of CYP34A has caused twentyfold elevation or greater elevation of blood levels of these statins.

For these reasons, the labeling of Posicor has been revised to state that coadministration of Posicor and lovastatin or simvastatin is contraindicated.

Metabolism of the calineurin immunosuppressants is dependent on CYP3A4, and the immunosuppressants in turn interfere with another mechanism (the P-glycoprotein drug transport system) that is important in processing all statins. As a result, three-way combination treatment with Posicor, a statin, and one of these immunosuppressants presents the risk of inappropriate accumulation of the statin and the consequent risk of rhabdomyolysis. Indeed, of the 7 patients who developed rhabdomyolysis during coadministration of Posicor and simvastatin, 4 were also receiving

cyclosporine.

Statin Cholesterol Drugs:

simvastatin (Zocor)-- Merck

lovastatin (Mevacor)-- Merck

atorvastatin (Lipitor)-- Pfizer Parke-Davis

cervistatin (Baycol)-- Bayer

fluvastatin (Lescol)-- Sandoz

pravastatin (Pravachol)-- Bristol Myers Squibb

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December 19, 1997
http://www.fda.gov/cder/news/posicor.htm

This is the retyped text of a letter from Roche Pharmaceuticals. Contact the company for a copy of any referenced enclosures.

December 1997

Dear Doctor:

We would like to inform you of important new warning information concerning the use of POSICOR (mibefradil dihydrochloride), a treatment for hypertension and chronic stable angina pectoris. This concerns:

1. a warning related to suppression of sinoatrial activity and severe bradycardia occurring with POSICOR, and
2. a warning and contraindication concerning drug interactions and statin-induced rhabdomyolysis with POSICOR and certain HMG-CoA reductase inhibitors.

This letter emphasizes the importance of patient selection, patient montoring, and attention to concomitant drug therapy to ensure that POSICOR is used appropriately. Please see enclosed complete product information.

I. Decreased Sinus Node Activity and Severe Bradycardia

The use of POSICOR has been associated with the appearance of symptomatic slow junctional rhythm. Ventricular rates have been as low as 30 to 40 bpm and many patients have been symptomatic. To date there have been about three dozen such reports arising from an exposure of 75,000 patients. This adverse effect has occurred mainly in elderly patients who were on concomitant beta-blocker therapy. Similar findings of symptomatic slow junctional rhythm have also been reported with other heart rate lowering compounds such as beta-blockers, digoxin, diltiazem and verapamil, especially when more than one of these agents are used at the same time.

In order to assist you in the appropriate use of POSICOR, please review the following package insert revision:

WARNINGS: ***Supression of Sinoatrial Node Activity:*** **Use of mibefradil has been associated with slowing or complete suppression of sinoatrial node activity. The supervening junctional rhythms have often been slow (as slow as 30 to 40 bpm). Many of the reports have incorrectly identified the adverse event as complete AV block. The reports have been most common in the elderly, mainly in association with the concomitant use of beta-blockers. Care should be taken when combining POSICOR with beta-blockers, particularly when pretreatment sinus rate is below 55 bpm, and this combination should be avoided in the elderly when pretreatment sinus rate is below 55 bpm (see PRECAUTIONS). In patients with low heart rates, use of any combination of agents that can slow the sinus node or affect the AV node (eg, beta-blockers, digitalis, and the calcium channel blockers mibefradil, diltiazem, and verpamil) should in general be undertaken only after careful consideration, as such combinations can unmask underlying sick sinus syndrome. Use of POSICOR in patients with**

sick sinus syndrome without a pacemaker is contraindicated (see CONTRAINDICATIONS).

POSICOR is associated with a dose related decrease in heart rate. This effect is achieved whether POSICOR is given as monotherapy or in combination with beta-blockers. In susceptible patients, as described in the revised warnings section, the decrease in sinus node activity may result in severe sinus bradycardia or sinus arrest. In reported cases, cardiac pacing has been taken over by the AV node, but sometimes at low rates that were poorly tolerated.

II. Interaction of POSICOR (mibefradil dihydrochloride) with certain HMG-CoA Reductase Inhibitors

Roche has received 7 domestic reports of statin-induced rhabdomyolysis in patients receiving simvastatin and POSICOR (4 of the cases were also receiving cyclosporine), presumably due to inhibition by POSICOR of the metabolism of simvastatin, markedly increasing simvastatin's plasma concentration. POSICOR is a strong inhibitor of cytochrome P450 3A4, the enzyme responsible for metabolizing several of the HMG-CoA reductase inhibitors. POSICOR also inhibits metabolism of cyclosporin, increasing its blood levels; cyclosporine itself decreases excretion of all HMG-CoA reductase inhibitors and substantially increases their blood levels.

POSICOR would be expected to have effects on blood levels of certain other HMG-CoA reductase inhibitors. Based on the similarity of lovastatin and simvastin metabolism, coadministration of POSICOR and lovastatin would also be expected to result in markedly increased plasma concentrations of lovastatin. Atorvastatin and cerivastatin are also metabolized by CYP450 3A4, but the metabolites are active, so the overall effect of POSICOR on their HMG-CoA reductase activity may not be large. Studies of atorvastatin and cervastatin with erythromycin, a moderate inhibitor of CYP450 3A4, have not shown marked increases in the blood levels of these HMG-CoA reductase inhibitors, but at present there are no studies with stronger inhibitors, such as mibefradil, ketoconazole, or itraconazole.

Since fluvastatin and pravastatin are not significantly metabolized by CYP450 3A4, POSICOR would not be expected to have a significant effect on their blood levels. Please see enclosed complete product information.

In order to assist you in the appropriate use of POSICOR, please review the following package insert revisions:

CONTRAINDICATIONS: POSICOR is contraindicated in patients who:

Are concurrently receiving terfenadine, astemizole, cisapride, lovastatin or simvastatin (see WARNINGS and PRECAUTIONS).

WARNINGS: ***Interaction Resulting in HMG-CoA Reductase Inhibitor-Induced Rhabdomyolysis:*** **Mibefradil inhibits the action of CYP450 3A4. When this enzyme is inhibited, plasma concentrations of those drugs that are metabolized by CYP450 3A4 may become elevated, sometimes by more than an order of magnitude (see PRECAUTIONS).**

Rhabdomyolysis is a known rare adverse effect of all of the HMG-CoA reductase inhibitors (the "statin" cholesterol-lowering agents).

The statins are not identically metabolized:

- Lovastatin and simvastatin are dependent on CYP450 3A4 for their metabolic clearance. Among

patients receiving simvastatin and mibefradil there have been reported cases of rhabdomyolysis. These events appear to reflect an incidence of rhabdomyolysis higher than that seen during treatment with simvastatin alone. Because of the metabolic similarities of lovastatin and simvastatin, coadministration of POSICOR with either of these two drugs is contraindicated.

- Atorvastatin and cerivastatin are biotransformed by CYP450 3A4 to active and inactive metabolites. Also, only small changes in HMG-CoA reductase inhibitor activity have been seen in studies where atorvastatin and cerivastatin were combined with erythromycin (a less potent CYP450 3A4 inhibitor than mibefradil). Nevertheless, until there is more information on the coadministration of CYP450 3A4 inhibitors (including mibefradil) with atorvastatin and cerivastatin, coadministration of either of these two drugs with POSICOR should generally be avoided.

- Fluvastatin and pravastatin are not significantly metabolized by CYP450 3A4; no clinically important interaction with mibefradil is anticipated. Therefore, no specific dose adjustment of fluvastatin or pravastatin is recommended with coadministration of POSICOR (mibefradil dihydrochloride).

Drug Interactions - Cyclosporine/Tacrolimus and HMG-CoA Reductase Inhibitors: The calcineurin immunosuppressants tacrolimus (FK-506) and cyclosporine are metabolized by CYP450 3A4, so their blood levels rise (in the case of cyclosporine, about twofold) when POSICOR is coadministered; dose adjustment may be necessary. Because the immunosuppressants themselves inhibit a drug-transport system that participates in the excretion of HMG-CoA reductase inhibitors, elevated levels of the immunosuppressants can cause additional elevations in the blood levels of any of the HMG-CoA reductase inhibitors. Use of POSICOR should be avoided in patients also receiving both a calcineurin immunosuppressant and an HMG-CoA reductase inhibitor.

We trust this information will assist you in using POSICOR to manage your hypertensive and angina patients appropriately. Please see enclosed complete product information.

If you have any questions about POSICOR, we encourage you to call the toll-free number for Roche Medical Services at 1-800-526-6367. Also, if you are aware of any serious adverse events potentially associated with the use of POSICOR, please report such information to Roche at the above number or the Food and Drug Administration MedWatch program at 1-800-FDA-1088.

Sincerely,

Russell H. Ellison, MD
Vice President
Medical Affairs

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